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09/990,099	11/21/2001	Scott A. Lesley	P0012US20	1291

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TIMOTHY L. SMITH
GENOMICS INSTITUTE OF THE
NOVARTIS RESEARCH FOUNDATION
10675 JOHN JAY HOPKINS DRIVE, SUITE E225
SAN DIEGO, CA 92121-1127

EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/990,099	Applicant(s) LESLEY ET AL.	
	Examiner Daniel M Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) *34-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *filing receipt* .

DETAILED ACTION

This is the First Office Action on the merits of the application filed 21 November 2001, which claims benefit of U.S. Provisional applications 60/324,833 filed 24 September 2001 and 60/327,575 filed 21 November 2000. The formal drawings filed 21 May 2002 and preliminary amendment filed 24 April 2003 have been entered. A corrected filing receipt is enclosed herewith. Claims 1-76 are presently pending in the application.

Election/Restrictions

Applicant's election of the invention defined by Group I, claims 1-33, wherein and the specific embodiments defined by SEQ ID NO: 21 and 23 and the *E. coli ibpA* promoter is acknowledged. Applicant states, "the restriction requirement is subject to the nonallowance of the linking claims 1 and 37. If a claim is found to be allowable with respect to the elected species of nucleic acid, the generic claim will then be examined" (page 6). Applicant has misstated the conditions of the restriction requirement with respect to the linking claims. According to standard linking claim practice, and as indicated on page 6 of the previous Office Action, the linking claims will be examined over their full scope along with the elected invention. If the linking claims are found allowable, each of the inventions encompassed by the linking claims will be examined (see MPEP §809).

Because the conditions of the restriction requirement are different from those set forth in the response, the election will be considered with traverse. Applicant's arguments

for traversal of the restriction requirement set forth in the 22 October 2002 response are addressed in Paper No. 14.

Claim 34-76, SEQ ID NO: 1-20, 22 and 24-46, and promoter regions from genes listed on Table 1 other than *E. Coli ipbA* are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12, filed 22 October 2002.

Double Patenting

It is noted that copending application 09/991,499 and 10/127,078 appear to contain closely related subject matter suggesting that the claims of 10/237,060 and this application may recite the same or overlapping Inventions. Since 09/991,499 and 10/127,078 are not presently available for review, no determination has been made as to whether or not a double patenting rejection over the claims should be applied to the claims of the instant application. If, upon availability of the above application to the Examiner, it is determined that there are conflicting claims between 09/991,499 or 10/127,078 and the instant application, double patenting will not be considered as new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-6 and 8-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims are directed to a host cell comprising a solubility reporter nucleic acid comprising a protein solubility responsive promoter operably linked to a reporter gene. The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 3, page 71434). In the instant case, the solubility responsive promoter is a critical functional element of the claimed subject mater and therefore must be adequately described in the specification. The specification defines "protein solubility responsive promoter" in paragraph [0028] as a promoter element that is either induced or repressed in a cell in response to an increased concentration of insoluble protein in the cytoplasm. Thus, the solubility responsive promoter of the claims encompasses a large and divergent genus of nucleic acid

molecules consisting of any and all prokaryotic, eukaryotic or viral promoters that respond to an increased concentration of insoluble protein in the cytoplasm of a cell. In some embodiments, the solubility responsive promoter is limited to comprising a nucleotide sequence that is at least 75% identical to the polynucleotide set forth as SEQ ID NO: 21 or 23 or an RpoH recognition site, or to promoters from various prokaryotes or eukaryotes.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In the instant case, the specification discloses 46 nucleic acid sequences having the function of a solubility responsive promoter based on induction or repression detected by GeneChip analysis. Although a substantial number of species are disclosed, the disclosed species do not adequately represent the tremendous scope of the genus. The Guidelines for Written Description state, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (*Id.*, at Column 2, page 71436). All of the species promoters disclosed are endogenous to a single prokaryotic organism, yet the claims encompass solubility responsive promoters from all other prokaryotic and eukaryotic cells, all species of organism. Given this enormous scope, it stands to reason that the structurally defined solubility responsive promoters disclosed in the instant application are not representative of the entire genus of solubility responsive promoters.

With regard to disclosure of relevant identifying characteristics, according to the Guidelines for written description, identifying characteristics include, "structure or other

physical and/or chemical properties...functional characteristics coupled with a known or disclosed correlation between function and structure or... a combination of such identifying characteristics..." (*Id.*, at column 3, second full paragraph). In the instant case, the specification identifies an RpoH recognition site as common to many solubility responsive promoters (paragraph [0060] and Figure 1). However, although the RpoH recognition site appears to be necessary for function of a subset of solubility responsive promoters (see Table 2), there is no evidence that it is sufficient for solubility responsiveness and, because it appears that many solubility responsive promoters do not comprise an RpoH recognition site, the presence or absence of an RpoH recognition site clearly does not identify a solubility responsive promoter. This would obviously be the case for solubility responsive promoters found in the numerous organisms that do not express an RpoH transcription factor. The claims also identify solubility responsive promoters as sequences having 75% identity to the disclosed solubility responsive promoters. Claiming the promoters in this way assumes that the mere sequence of nucleotides that make up a nucleic acid is the relevant identifying characteristic of the molecule. However, the primary structure of a nucleic acid is a relevant identifying characteristic only insofar as that structure can be correlated with a function. The skilled artisan would understand that it is the function of a nucleic acid that is the relevant identifying characteristic of the molecule because it is the function, not the structure, which has utility. Clearly a recitation of primary structure does not provide the relevant identifying characteristics of the claimed molecules because the vast majority of the molecules that meet the structural limitation would not have the same function as the nucleic acids set forth in the application. If the instant disclosure had described the

nucleic acids such that the skilled artisan could distinguish, or envision molecules encompassed by the structural limitations of the claims having a defined function from those molecules that are non-functional, the written description requirement would be satisfied. In contrast, the instant disclosure provides a description of structure with no correlation of structure with function. Because the teachings of the specification provide no means by which the skilled artisan could envision those nucleic acids encompassed within the genus of nucleic acids having 75% identity with the disclosed nucleic acids and that also have a defined function, the disclosure fails to teach the relevant identifying characteristics of said genus.

Finally, Applicant has set forth methods for identifying solubility responsive promoters not described in the specification. However, an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property, i.e., it has the function of a solubility responsive promoter, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of solubility responsive promoters. Therefore, only the described promoters comprising the sequences set forth as SEQ ID NO: 1-46 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 8, 11, 14-18, 22-25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Farr U.S. Patent No. 5,589,337 (made of record in the IDS filed 7 November 2002).

Claim 1 is directed to a host cell comprising a solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene and a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide, wherein expression of the target polypeptide in an insoluble for causes a change in expression of the reporter gene. It is noted that the disclosure does not define the target polypeptide-expressing nucleic acid in such a way as to exclude

endogenous genes. Therefore, the art is applied insofar as the claims encompass a target polypeptide-expressing nucleic acid that is endogenous to the host cell. Farr teaches a host cell comprising a solubility responsive promoter operably linked to a reporter gene wherein expression of a target polypeptide in an insoluble form causes a change in expression of the reporter gene (see especially the third and fourth full paragraphs in column 2, the third paragraph in column 4 and line 3 in column 5). Because the host cell of Farr further comprises endogenous genes that meet the limitation of a target polypeptide-expressing nucleic acid, the host cell of Farr anticipates all of the limitations of the base claim, claim 1.

Farr further teaches the host cell: wherein the solubility responsive promoter comprises an RpoH recognition site (i.e., dnaK promoter; column 9, first full paragraph) according to claim 5; wherein the solubility responsive promoter is upregulated in the presence of insoluble target protein (i.e., dnaK promoter, *Id.*; lon promoter and clpB promoter, column 8, second full paragraph) according to claim 8; wherein the target protein expressing nucleic acid comprises a promoter linked to the target protein encoding polynucleotide according to claim 11; wherein the solubility promoter is from *E. coli* according to claims 14-18, which is the same species as the host cell according to claim 28; and wherein any one of a variety of reporter genes are used according to the limitations of claims 22-27 (see especially column 11).

Farr teaches each of the limitations of the claimed host cell; therefore, Farr anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11, 14-18, 22-25 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr as applied to claims 1, 5, 8, 11, 14-18, 22-25 and 28 above, and further in view of Allen *et al.* (1992) *J. Bacteriol.* 174:6938-6947.

The teachings of Farr are described herein above. Farr does not teach a solubility responsive promoter comprising the sequence set forth as SEQ ID NO: 21 or 23

according to claims 2, 3, 6 and 7, or a regulatory region from the ibpA gene according to claim 4. Allen *et al.* teaches the promoter region from the *E. coli* ibpA gene, which comprises a nucleic acid sequence that is 100% identical to the instant SEQ ID NO: 21 and 23 (see especially the attached sequence alignments). Allen *et al.* further teaches that the ibpA gene is likely responsive to the presence of a high level of unfolded proteins (see especially the second full paragraph in the second column on page 6945).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use the solubility responsive promoter taught by Allen *et al.* in the host cell of Farr according to the limitations of the instant claims 2-4, 6 and 7.

Motivation to combine these teachings comes from Allen *et al.*, who teaches that the ibpA gene regulatory region is a heat shock promoter that is responsive to protein stresses such as misfolding, and from Farr who teaches that promoters that respond to protein stress are useful in the invention disclosed therein (see especially the third paragraph in column 4, the second full paragraph in column 8 and the first full paragraph in column 9). Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because the methods set forth in Farr will work with any stress regulated promoter.

Conclusion

Claims 9, 10, 12, 13, 19-21 and 29-33 are free of the art of record. The art does not teach or suggest a host cell comprising a solubility reporter nucleic acid and a target-polypeptide expressing nucleic acid; wherein the solubility responsive promoter is downregulated according to claim 9; wherein the target-polypeptide expressing nucleic

acid comprises a promoter or polypeptide encoding nucleic acid that is heterologous to the host cell or to the other component of the target-polypeptide expressing nucleic acid according to claims 10, 12 and 13; wherein the solubility responsive promoter is from a gram positive bacterium or eukaryote according to claims 19-21; or wherein the target polypeptide comprises a fragment or mutated form of a polypeptide according to claims 29-33.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
June 4, 2003

JAMES KETTER
PRIMARY EXAMINER